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Application of: Kroczek, Richard

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Application No.: 10/647,072

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For: TREATMENT OF IMMUNE DISORDERS WITH ANTIBODIES TO COSTIMULATING POLYPEPTIDE OF T CELLS

Attorney Docket No.: 7853-267

DECLARATION OF RICHARD KROCZEK UNDER 37 C.F.R. § 1.132

U.S. Patent and Trademark Office
PO Box 1450
Alexandria, Virginia 22313-1450

Sir:

I, RICHARD KROCZEK do declare and state:

1. I am the inventor of the invention described and claimed in the above-identified patent application (the "'072 application").

2. I presently hold the position of Professor of Molecular Immunology at the Robert Koch Institute, Berlin, Germany, the assignee of the above-identified patent application. My *curriculum vitae* is attached hereto as Exhibit 1.

3. I have read and am familiar with the '072 application.

4. The invention claimed in the '072 application is directed to methods of treating immune disorders (claim 77) and autoimmune disorders (claim 78) comprising administering monoclonal antibodies directed against the human 8F4 polypeptide. Since the original filing date of the '072 specification, the 8F4 polypeptide has come to be referred to in the literature as "ICOS" (Inducible T cell Co-Stimulator).

5. Described in paragraphs 6 to 39 below are a number of studies that demonstrate an involvement of the ICOS pathway in a spectrum of immune and autoimmune

disorders. These studies demonstrate that inhibition of the ICOS pathway in accepted animal models for a variety of immune and autoimmune human diseases results in amelioration of the respective diseases, such as inflammatory bowel disease, systemic lupus erythomatosus, and rheumatoid arthritis. In addition, for some disease, additional studies are described below that demonstrate the role of ICOS in the pathology of a variety of immune and autoimmune diseases in humans. The studies described below thus corroborate the teachings provided in the application by indicating that successful *in vivo* amelioration of immune disorders and autoimmune disorders can be achieved by administration of anti-ICOS antibodies.

**ICOS INVOLVEMENT IN INFLAMMATORY BOWEL DISEASE**

6. Inflammatory bowel disease ("IBD") is a group of inflammatory conditions of the large intestine and, in some cases, the small intestine. The main forms of IBD are Crohn's disease ("CD") and ulcerative colitis ("UC"), also known as chronic colitis.

7. Several animal models of chronic colitis have been established, including a mouse model involving the adoptive transfer of CD4+CD45RB$^{high}$ native T cells from BALB/c mice to syngeneic SCID mice. In this murine model, the recipient mice develop symptoms similar to IBD (Totsuka *et al.*, 2003, Gastoenterology 124:410-421 ("Totsuka") at page 410). In this murine model, administration of anti-ICOS antibodies to the SCID recipient mice ameliorated chronic colitis both during the establishment and following onset of the disease (see Totsuka at Abstract, under "Results" and page 413, right column). The observations of Totsuka, among other studies in the literature, led Kanai *et al.*, 2002, J. Gastroenterol. 37[Suppl. XIV]:78-81 to propose ICOS as a therapeutic target for human IBD patients (see, *e.g.*, Kanai at Abstract).

8. Sato *et al.*, 2004, Gastroenterology 126:829-39 ("Sato") analyzed the expression and role of ICOS in UC and CD in human patients. Sato demonstrated that ICOS-

expressing CD4+ lamina propria T cells ("LPTC") were significantly increased in the inflammatory mucosa patients with active, but not inactive, UC and CD as compared to a normal control (see Sato at Abstract; page 832, right column; and page 836, right column). ICOS stimulation also enhanced production of certain cytokines by UD and CD (see Figure 6 and page 836, right column). Because the ICOS upregulation observed by Sato was limited to the inflammatory sites of IBD, ICOS is proposed to be an "ideal" therapeutic target for IBD (Sato at Abstract; page 836, right column; and page 838, right column).

9. Taken together, Totsuka, Kanai and Sato strongly indicate that: a) ICOS participates in the pathogenesis of IBD in humans; and b) treatment of IBD can be achieved by inhibiting the ICOS pathway, such as by administration anti-ICOS antibodies, in patients suffering from IBD.

**ICOS INVOLVEMENT IN SYSTEMIC LUPUS ERYTHEMATOSUS DISEASE.**

10. Systemic lupus erythematosus ("SLE") is a chronic inflammatory disease whose patients exhibit different immunological abnormalities, including the production of autoimmune antibodies, lack of T- and B-cell regulation, and defective clearance of autoantigens and immune complexes. SLE has manifestions in the kidneys, central nervous system, and skin (see, *e.g.*, the backgrounds of (Hutloff *et al.*, 2004, Arthritis and Rheumatism 50(1):3211-3220 ("Hutloff"); Yang *et al.*, 2005, Rheumatology e-publication doi:10.193/rheumatology/keh724 ("Yang"); and Iwai *et al.*, 2003, J. Immunol. 171:2848-54 ("Iwai").

11. Iwai studied the role of the ICOS pathway in a mouse model of SLE, murine lupus nephritis, which reflects the renal pathology of SLE. SLE and murine lupus nephritis both are characterized in the deposition of autoimmune antibodies in the kidneys. Iwai studied the expression of ICOS on T cells from NZB/W $F_1$ mice, which spontaneously develop murine lupus nephritis, before and after onset of the disease. Iwai observed the

ICOS expression on T cells from splenocytes and on peripheral blood lymphocytes increase with age, and occurs on almost all T cells by the onset of the disease (Iwai at 2849, right paragraph). Inhibition of the ICOS pathway by use of an antibody against the ICOS ligand ("ICOS-L"), B7RP-1 (also known as B7h), prevented disease onset and, following cessation of treatment, some symptoms of the disease developed, but with a markedly improved disease course (Iwai at page 2850). In addition, treatment of mice with the anti-B7RP-1 antibody following onset of the disease improved the symptoms of the disease and survival rate (Iwai at pages 2851-52)[1]

12. Hutloff and Yang, which document the involvement of ICOS in SLE in humans, further confirm the role of ICOS in the pathology of the disease. Hutloff is a publication of a study performed in my laboratory to determine the expression levels of ICOS in patients with SLE. The data showed that ICOS is expressed in CD4+ and CD8+ T cells and a concomitant downregulation of ICOS Ligand (ICOS-L) on B cells of such patients. Our study also indicated that the downregulation of ICOS-L is a result of the interaction of ICOS+ T cells with the B cells. In addition, we observed clusters of B cells and plasma cells in close contact with ICOS + T cells in the kidneys of SLE patients. These data strongly indicate that ICOS is an important driving force in the pathogenesis of SLE.

13. Similar results to those of the Hutloff publication were obtained by Yang. In addition, Yang showed that inhibition of the ICOS pathway in peripheral blood mononuclear cells from patients with SLE inhibited the production of pathological anti-DNA antibodies (Yang at pages 7-8 and Figure 4). These data further confirm that the activation of the ICOS pathway in SLE patients is involved in the pathology of SLE.

[1] Although Iwai did not see any therapeutic benefits of an anti-ICOS antibody, further analysis of the anti-ICOS antibody employed in Iwai's studies demonstrated that it was an agonistic, rather than an antagonistic, antibody (Iwai at page 2852, right column).

14. Taken together, Iwai, Hutloff and Yang strongly indicate that: a) ICOS participates in the pathogenesis of SLE in humans; and b) treatment of SLE can be achieved by inhibiting the ICOS pathway, such as by administration of anti-ICOS antibodies, in patients suffering from SLE.

**ICOS INVOLVEMENT IN RHEUMATOID ARTHRITIS.**

15. Rheumatoid arthritis ("RA") is a chronic inflammatory joint disease (see background sections of Okamoto *et al.*, 2003, J. Rheumatology 30:1157-63 ("Okamoto"); Nurieva *et al.*, 2003, J. Clin. Invest. 111:701-06 ("Nurieva"); and Iwai *et al.*, 2002, J. Immunol. 169:4332-4339 ("Iwai 2"). Collagen-induced arthritis ("CIA") is the most widely used mouse model for RA (see, *e.g.*, Nurieva at Introduction).

16. ICOS expression is observed in inflammatory tissue involved in CIA, such as synovium and lymph nodes (Iwai 2 at page 4335). Blocking the ICOS pathway using an antibody against B7RP-1 beginning at disease induction "significantly ameliorated the clinical manifestations of CIA in a dose dependent manner" (Iwai 2 at page 4334, left column). Furthermore, blocking the ICOS pathway after onset of the disease was also "effective at reducing the clinical arthritis scores" (*i.e.*, effective at reducing severity of the disease) (Iwai 2 at page 4334, right column). This study demonstrates a therapeutic potential for blocking the ICOS pathway, for example by using an anti-ICOS antibody, in RA.

17. The role of ICOS in CIA was further confirmed by Nurieva's study[2] analyzing the ability of ICOS knockout mice to develop CIA. Nurieva observed that the ICOS knockout mice were completely resistant to CIA (Nurieva at page 703). This study

[2] Although Nurieva was subsequently retracted (J. Clin. Invest. 112:1597), the reason of the retraction was that the study had not been performed with the permission of the University of Washington Institutional Animal Care and Usage Committee; however, the data in the publication are still valid.

corroborates the conclusion drawn from Iwai 2 that blocking the ICOS pathway, for example by using an anti-ICOS antibody, has a therapeutic potential for RA.

18. Okamoto confirms the role of ICOS in the pathology of arthritis in humans. Specifically, Okamoto is a study of ICOS (also referred to by Okamoto as H4) expression and function in human rheumatoid arthritis, and demonstrates that ICOS is overexpressed in the mononuclear cells of peripheral blood of RA patients as compared to healthy individuals, and also in synovial fluid of RA patients (Okamoto at page 1161, right column). The ICOS ligand B7RP-1 is also expressed in synovial tissues of patients (Okamoto at page 1161, right column). Based on these results and others, Okamoto suggests that the expression of ligand in synovial tissue activates ICOS in synovial fluid T cells, resulting in induction of proinflammatory cytokine expression and RA disease pathology (Okamoto at page 1161, right column and page 1162).

19. Taken together, Iwai 2, Nurieva and Okamoto demonstrate that: a) ICOS participates in the pathogenesis of RA in humans; and b) amelioration of RA symptoms in humans can be achieved by blocking the ICOS pathway, such as by administration of anti-ICOS antibodies.

## ICOS INVOLVEMENT IN AUTOIMMUNE MYOCARDITIS

20. Myocarditis is the inflammation of the myocardium, the muscular part of the heart. The origins of myocarditis are often autoimmune reactions to cardiac myosin (see, *e.g.*, Matsui *et al.*, 2003, Human Gene Therapy 14:521-32 ("Matsui") at Introduction and Futamatsu *et al.*, 2003, Cardiovascular Research 59:95-104 ("Futamatsu") at Introduction).

21. Experimental autoimmune myocarditis ("EAM") is a rat model of myocarditis that involves immunization of rats with cardiac myosin (see Introductions of Matsui and Futamatsu). There are two phases of EAM: an antigen priming phase (days 0-14) and an immune response phase (days 14-21) (see Futamatsu at background). Matsui and Futamatsu

used different approaches to block the ICOS pathway in EAM: Matsui employed an adenoviral expression vector of soluble ICOS (which is a competitive inhibitor of the binding of native ICOS to its ligand) and Futamatsu employed an anti-ICOS antibody and soluble ICOS ligand (which is a competitive inhibitor of the binding of native ICOS ligand to ICOS).

22. In Matsui's study, increased expression of ICOS and its ligand in lymphoid tissue of EAM rats was observed (see, *e.g.*, Figure 2). Administration of the soluble ICOS adenoviral vector resulting in expression during the first phase of EAM had little therapeutic benefit; however, administration of the vector resulting in expression during the second phase of EAM ameliorated the symptoms of the disease (see, *e.g.*, Table 1 and Figure 5) and improved the survival rate of the animals (see Table 2). Matsui concludes that blockade of the ICOS pathway had therapeutic potential for ongoing autoimmune myocarditis (Matsui at Abstract and Overview Summary).

23. Futamatsu observed similar results. ICOS was detected on myocardial inflammatory cells (page 98, left column). Blockade of the ICOS pathway in the first phase of EAM also had little therapeutic benefit while treatment during the second phase improved disease symptoms (see, *e.g.*, Figures 3 and 4). Futamatsu concludes that blockade of the ICOS pathway may have potential therapy for myocarditis (see Abstract and page 103, right column).

## ICOS INVOLVEMENT IN MYASTHENIA GRAVIS

24. Myasthenia gravis is a chronic autoimmune neuromuscular disease, characterized by varying degrees of weakness of the skeletal muscles, that results from autoantibodies to the nicotinic acetylcholine receptors ("AChRs) of the neuromuscular junction (see, *e.g.*, Scott *et al.*, 2004, J. Neuroimmunology 153:16-25 ("Scott") at Introduction).

25. Scott studied the role of ICOS in a mouse model of myasthenia gravis, experimental autoimmune myasthenia gravis ("EAMG"), by analyzing the development of the disease in ICOS knockout mice. EAMG is induced by immunization with AChR protein. Unlike normal mice, which develop symptoms that accurately mimic the pathogenesis of myasthenia gravis in response to immunization with AChR protein (Scott at Introduction), ICOS knockout mice were highly resistant to clinical experimental autoimmune myasthenia gravis (Scott at Abstract). Scott's results strongly suggest a therapeutic potential for the treatment of myasthenia gravis in humans by blocking the ICOS pathway, for example by use of an anti-ICOS antibody.

**ICOS INVOLVEMENT IN AUTOIMMUNE UVEORETINITIS**

26. Uveitis is inflammation inside the eye, specifically affecting one or more of the three parts of the eye that make up the uvea: the iris, the ciliary body, and the choroid.

27. Usui *et al.*, 2006, Eur. J. Immunol. 36:3071-81 ("Usui") studied the role of ICOS in a mouse model of uveitis, experimental autoimmune uveoretinitis ("EAU"), by blocking the ICOS pathway at different stages of the disease. EAU is induced by immunization with interphotoreceptor retinoid-binding protein ("IRBP"). Normal mice develop a histopathology that accurately mimic the pathogenesis of myasthenia gravis in response to immunization with IRBP (Usui at page 3072). Following induction of EAU in mice, ICOS is expressed on ocular infiltrating CD4+ T cells and expression of its ligand B7RP-1 is upregulated in ocular tissue (Usui at Figures 1 and 2). Disease progression was limited in ICOS knockout mice (Figure 3D-3F), and blocking the ICOS pathway with an antibody against B7RP-1 ameliorated the symptoms of the disease (Figure 3A-3C). Blockade of the pathway was effective in the second (effector) stage of EAU but not the first (induction) stage. Usui's results strongly suggest a therapeutic potential for the treatment of uveitis in humans by blocking the ICOS pathway, for example using anti-ICOS antibodies.

## ICOS INVOLVEMENT IN ATOPIC DERMATITIS

28. Atopic dermatitis ("AD"), also called eczema, is a highly prevalent chronic inflammatory skin disease characterized by inflammatory cell infiltration in the skin (Chen *et al.*, 2004, Clinical and Experimental Immunology 139:189-201 ("Chen") at Summary and Introduction).

29. Chen employed a transgenic IL-4 mouse model, in which the mice are characterized by spontaneous development of chronic inflammatory symptoms closely resembling human AD, to analyze of the role of ICOS at different stages of the disease: (1) prior to onset, (2) early or acute lesion, and (3) late or chronic lesion. Chen observed the expression of ICOS increase in secondary lymphoid organs during disease progression (see Figure 1), suggesting a role for ICOS in disease progression and implicating ICOS as a potential therapeutic target for AD.

## ICOS INVOLVEMENT IN MULTIPLE SCLEROSIS

30. Multiple sclerosis is a chronic, inflammatory, demyelinating, autoimmune disease that affects the central nervous system.

31. Experimental allergic encephalomyelitis (EAE) is the primary recognized animal model of multiple sclerosis. EAE is initiated by immunizing susceptible strains of mice with specific myelin proteins such as proteolipid protein peptide (PLP) 139-151. The immune response to the myelin antigens can be divided into afferent and efferent phases. During the afferent phase, myelin antigens are "processed" by antigen presenting cells (APCs) in regional lymph nodes and presented in the context of major histocompatibility class II (MHC II) molecules to naïve myelin-specific CD4+ T cells. The interaction of the MHC II molecule with the T cell receptor (TCR) sends an activation signal to the cell, ultimately resulting in differentiation into an encephalitogenic effector T cell. During the efferent phase of the disease, the encephalitogenic T cells traffic to the brain and are further

activated in situ through the TCR to mediate disease (see, *e.g.*, Rottman *et al.*, 2001, Nat Immunol. 2(7):605-11 ("Rottman") at background).

32. In Rottman, mice in which experimental EAE was induced were treated with a blocking anti-ICOS antibody either during antigen priming (days 1-10) or during the efferent immune response to PLP (days 9-20). Although blockade of the ICOS pathway during antigen priming (1-10 days after immunization) exacerbated disease, ICOS blockade during the efferent immune response (9-20 days after immunization) abrogated disease (see Rottman at Abstract).

33. In my opinion, although the timing of treatment is important to maximize its therapeutic efficacy, blocking the ICOS pathway using anti-ICOS antibodies is a promising clinical approach for treatment of multiple sclerosis.

## ICOS INVOLVEMENT IN ORGAN TRANSPLANT REJECTION

34. Several animal studies indicate that blocking the ICOS pathway, for example, using anti-ICOS antibodies or soluble ICOS ligand, results in improved survival of organ transplants.

35. For example, Ozkaynak *et al.*, 2001, Nat. Immunol. 2(7):591-96 is one study that describes the inhibition of the ICOS pathway by an anti-ICOS monoclonal antibody or an ICOS polypeptide in the context of organ transplant rejection. The data presented in Ozkaynak demonstrate that the administration of an anti-ICOS antibody or a soluble ICOS polypeptide to an organ transplant recipient leads to inhibition of organ transplant rejection and prolongation of graft survival from approximately one week to almost three weeks (Figure 2). Similar prolongation of graft survival was observed in ICOS deficient mice, further evidencing a role for ICOS in rejection of the transplant.

36. Similarly, a study by Nakamura *et al.*, 2003, Transplantation 75(8):1115-8 ("Nakamura") demonstrates that treatment of a mouse recipient of an islet allograft with an

anti-ICOS antibody prolonged islet allograft survival. Moreover, when the anti-ICOS antibody treatment was administered as part of a regimen further including an immunosuppressive agent, not only was graft survival prolonged, but the regimen also increased the survival of the experimental animals at 90-days post transplant to 50%, from 0% in untreated animals and 11% in animals treated with a comparable dosage of immunosuppressive reagent. These data lead the Nakamura authors to conclude that "ICOS has an essential role in rejection of intrahepatic islet allografts and the blockade of ICOS interaction might be a novel approach for preventing islet allograft rejection" (Nakamura at Abstract).

37. Harada *et al.*, 2003, J. Clin. Invest. 112(2):234-43 ("Harada"), describes experiments testing the effect of blocking the ICOS pathway at different times following transplantation of cardiac allografts (early treatment and delayed treatment) in experimental animals with different immune make ups (recipient animals whose minor histocompatibility antigen matched that of the donor and recipient animals whose minor histocompatibility antigen mismatched that of the donor). Harada demonstrates a beneficial effect of administration of disrupting the ICOS pathways in three out of the four experimental set ups described: both early and delayed treatment in the minor histocompatibility mismatched animals, and in the delayed treatment in the minor histocompatibility matched animals (see Figure 1 on page 236 of Harada). In one group, the histocompatibility matched animals receiving an early anti-ICOS antibody treatment, the early treatment accelerated graft rejection (Figure 1). The authors of Harada conclude that, overall, blocking the ICOS pathway is an effective means of prolongation of graft survival (see, *e.g.*, the last paragraph of the Discussion on page 242 of Harada), although the timing of treatment is important to maximize its therapeutic efficacy.

38. Thus, despite the limited circumstances under which blocking the ICOS pathway accelerated graft rejection, it is my belief that blocking the ICOS pathway using anti-ICOS antibodies is a promising clinical approach for treatment of organ transplant rejection.

## ICOS INVOLVEMENT IN ASTHMA

39. I have previously described experiments evidencing the role of ICOS in asthmatic disorders by way of a declaration in connection with U.S. Patent Application No. 09/972,524 (now U.S. Patent No. 7,125,551). Based on the evidence presented in that Declaration, attached hereto as Exhibit 21, I concluded that "a) ICOS participates in the pathogenesis of allergic asthma in human; and b) amelioration of asthma symptoms in human can be achieved by administration of antibodies that recognize the ICOS polypeptide." Exhibit 21 at ¶ 14.

## CONCLUSION

40. The studies described herein implicate ICOS in a wide spectrum of immune and autoimmune diseases. The animal models of disease employed in the studies are the best approximations of the corresponding human diseases known to the scientific community and are used by the pharmaceutical industry in preclinical studies of clinical candidates. The data obtained from the studies described above strongly indicate that treatment of a number of such diseases can be achieved by inhibiting the ICOS pathway, for example by use of an anti-ICOS antibody. Indeed, on the basis of studies such as those described herein, MedImmune Inc. has licensed an anti-ICOS antibody from Japan Tobacco Inc. for development as an anti-inflammatory therapeutic for autoimmune disorders SLE and RA (see, *e.g.*, Exhibit 22, Bioworld Today December 29, 2006 at pages 1-2). It is also my opinion that most, if not all, inhibitory anti-ICOS antibodies will exhibit some efficacy towards treatment of such diseases, and that optimization of any given antibody for clinical use (*e.g.*, by chimerization

or humanization and/or improvement of the binding kinetics by mutagenesis of the antibodies' complementarity determining regions) could have been performed as of September 1997 using standard methodologies.

41. I declare further that all statements made in this Declaration of my own knowledge are true and that all statements made on information and belief are believed to be true and further that these statements are made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Dated: May 2, 2007

Richard Kroczek

Attachments:

Exhibit 1. *Curriculum vitae* of Richard Kroczek, M.D.

Exhibit 2. Totsuka *et al.*, 2003, Gastoenterology 124:410-421

Exhibit 3. Kanai *et al.*, 2002, J. Gastroenterol. 37[Suppl. XIV]:78-81

Exhibit 4. Sato *et al.*, 2004, Gastroenterology 126:829-39

Exhibit 5. Hutloff *et al.*, 2004, Arthritis and Rheumatism 50(10):3211-3220

Exhibit 6. Yang *et al.*, 2005, Rheumatology e-publication doi:10.193/rheumatology/keh724

Exhibit 7. Iwai *et al.*, 2003, J. Immunol. 171:2848-54

Exhibit 8. Okamoto *et al.*, 2003, J. Rheumatology 30:1157-63

Exhibit 9. Nurieva *et al.*, 2003, J. Clin. Invest. 111:701-06

Exhibit 10. Iwai *et al.*, 2002, J. Immunol. 169:4332-39

Exhibit 11. Nurieva *et al.*, 2003, J. Clin. Invest. 112:1597

Exhibit 12. Matsui *et al.*, 2003, Human Gene Therapy 14:521-32

Exhibit 13. Futamatsu et al., 2003, Cardiovascular Research 59:95-104

Exhibit 14. Scott *et al.*, 2004, J. Neuroimmunology 153:16-25

Exhibit 15. Usui *et al.*, 2006, Eur. J. Immunol. 36:3071-81

Exhibit 16. Chen *et al.*, 2004, Clinical and Experimental Immunology 139:189-201

Exhibit 17. Rottman *et al.*, 2001, Nat. Immunol. 2(7):605-11

Exhibit 18. Ozkaynak *et al.*, 2001, Nat. Immunol. 2(7):591-96

Exhibit 19. Nakamura *et al.*, 2003, Transplantation 75(8):1115-8

Exhibit 20. Harada *et al.*, 2003, J. Clin. Invest. 112(2):234-43

Exhibit 21. Kroczek Rule 132 Declaration in connection with U.S. Patent Application No. 09/972,524.

Exhibit 22. Bioworld Today, December 29, 2006 edition.

# CURRICULUM VITAE


**Name:** Richard Kroczek, M.D.

**Occupation:** Professor, Molecular Immunology
Robert Koch-Institute
Nordufer 20, 13353 Berlin, Germany

**Phone:** (+49) 30 4547-2450
**Fax:** (+49) 30 4547-2603
**e-mail:** kroczek@rki.de


**Personal Information:** born November 3, 1952 in Orlau
Nationality: German

**Education and Training:**

| | |
|---|---|
| 1964 - 1973 | Attending the Hans-Leinberger-Gymnasium in Landshut, Germany; graduated first in the class of 1973 |
| 1973 - 1976 | Pre-clinical studies at the University of Kiel |
| 1976 - 1977 | Medical School, University of Bonn |
| 1977 - 1978 | Westminster Hospital Medical School, London, supported by a grant from the Deutscher Akademischer Austauschdienst |
| 1978 - 1981 | Continuation of clinical studies at the University of Bonn |
| 1981 | Final Medical Exam ("Staatsexamen"); Doctoral thesis; Medical License |
| 1981 - 1983 | Residency in Pediatrics at the Munich University Children's Hospital |
| 1983 | American Medical Exam (VQE) |
| 1984 - 1986 | Postdoctoral Fellow in Immunology with Dr. Ethan Shevach in the Laboratory of Allergy and Infectious Diseases, NIH, USA. Supported by a grant from the Deutsche Forschungsgemeinschaft. Research topics: Role of Thy-1 in T-cell activation, action of cyclosporin A |
| 1986 | Research fellow of the Fogarty Foundation |

| | |
|---|---|
| 1986 - 1987 | Postdoctoral fellow at the Max-Planck-Institute for Immunobiology in Freiburg |

**Employment:**

| | |
|---|---|
| 1987 - 1992 | Head of a research group at the Max-Planck-Society Research Unit for Immunology in Erlangen, Germany |
| 1990 | Habilitation at the University of Erlangen; faculty member of the university |
| 1997 | Professor, University of Erlangen |
| 1993 - | Head, Molecular Immunology, Robert Koch-Institute, Berlin |
| 1999 | Offered chair in immunology at the Free University of Berlin (not accepted) |

**Current research:** Molecular mechanisms of early T cell activation, T cell/B cell cooperation, T cell/monocyte cooperation, T cell/dendritic cell cooperation focus on the function of CD40 Ligand, ATAC and ICOS molecules in vitro and in vivo

**Professional and scientific activities:**

Member of the German Society for Immunology.

Reviewer for various scientific journals (European Journal of Immunology, Journal of Immunology, European Journal of Biochemistry, Blood, Journal of Clinical Investigation, Nature Medicine).

Reviewer for various scientific societies and funding agencies.

**Honors:**

Science prize of the SmithKline Beecham Foundation 1999.

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